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(71) Applicants *(for all designated States except US)*: THE GENERAL HOSPITAL CORPORATION [US/US]; 55 Fruit Street, Boston, MA 02114 (US). TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK [US/US]; 500 West 120th Street, New York, NY 10027 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HAUPERT, Garner, T., Jr. [US/US]; 512 Great Road, Littleton, MA 01460 (US). NAKANISHI, Koji [JP/US]; Apartment 9J, 560 Riverside Drive, New York, NY 10027 (US). AKRITOPOULOU-ZANZE, Irini [GR/US]; Apartment 6D, 530 Riverside Drive, New York, NY 10027 (US).

(74) Agents: ELMORE, Carolyn, S. et al.; Hamilton, Brook, Smith & Reynolds, P.C., Two Militia Drive, Lexington, MA 02173 (US).

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(54) Title: NOVEL OUABAIN ANALOGS

(57) Abstract

A method of treating cardiac malfunction by administering a positive inotropic effect-producing amount of a compound as described herein.

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NOVEL OUABAIN ANALOGS

Background of the Invention

Digitalis, digoxin, ouabain and related substances are cardiac glycosides derived from plants. The main pharmacokinetic property of cardiac glycosides is the ability to increase the force of myocardial contraction in a dose dependent manner (positive inotropic effect). The most probable explanation for the direct positive inotropic effect is the ability of cardiac glycosides to inhibit membrane-bound Na^+, K^+-activated adenosine triphosphatase (Na^+, K^+-ATPase) (Hoffman, B.F. and J.T. Bigger, Jr., "Digitalis and Allied Cardiac Glycosides" in The Pharmacological Basis of Therapeutics, eds. Goodman and Gilman, p. 732, (1980)). The hydrolysis of adenosine triphosphate (ATP) by this enzyme provides the energy for the sodium potassium pump.

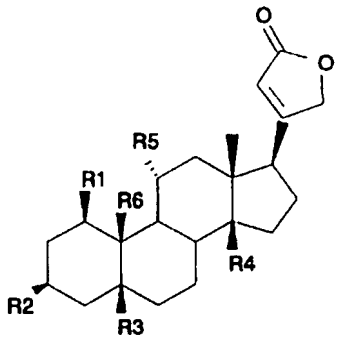
Because of their positive inotropic effect, cardiac glycosides (e.g., digitalis and ouabain) are unrivaled in value for the treatment of heart failure. Cardiac glycosides are most frequently used therapeutically to increase the adequacy of the circulation in patients with congestive heart failure and to slow the ventricular rate in the presence of atrial fibrillation and flutter.

However, cardiac glycosides have narrow therapeutic indices and their use is frequently accompanied by toxic effects that can be severe or lethal. The most important toxic effects, in terms of risk to the patient, are those that involve the heart (e.g., abnormalities of cardiac rhythm and disturbances of atrio-ventricular conduction). Gastrointestinal disorders, neurological effects, anorexia, blurred vision, nausea and vomiting are other common

cardiac glycoside-induced reactions. As such, there is a need to develop cardiac glycosides which do not possess these problems.

SUMMARY OF THE INVENTION

The present invention relates to novel ouabain derivatives useful in producing a positive inotropic effect in mammals, and intermediates in the production of these compounds. The compounds of the present invention possess the formula:



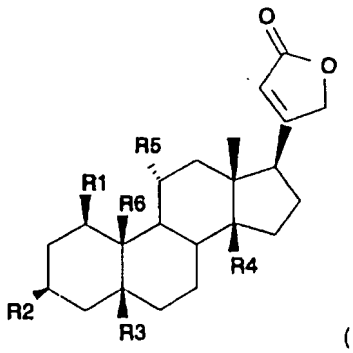
(I)

wherein each of R1-R6 is independently selected from the group consisting of OH, acyloxy, and rhamnosyl. Thus, the invention comprises, in one embodiment, a method for producing a positive inotropic effect in a mammalian host by administering to said host a positive inotropic effect-producing amount of the compounds described herein.

This invention further relates to the administration of the compounds to treat cardiac glycoside intoxication, edematous disorders and hypotension. Also, the compounds can be used to develop specific therapies to prevent hypertension.

DETAILED DESCRIPTION OF THE INVENTION

As set forth above, the compounds of the claimed invention possess the formula:



(I)

wherein each R1, R3, R4, R5 and R6 is selected from the group consisting of OH, acyloxy and/or rhamnosyl. Preferably, at least one of R1, R3, R4, R5 and R6 is rhamnosyl. R2 is OH or acyloxy. The acyloxy group serves as a protecting group for the hydroxy moiety in preparing and testing the compounds described herein. The acyloxy group can be derived from a carboxylic acid, carbamic acid, oxamic acid, sulfonic acid or phosphorous acid, for example, and can be aliphatic, cycloaliphatic or aromatic. The aliphatic acid preferably has between 1 to about 20 carbons, more preferably between 1 and about 4 carbons and can be substituted or unsubstituted, saturated or unsaturated. Cycloaliphatic acids can be heterocyclic or carbocyclic, saturated or unsaturated, monocyclic or polycyclic, substituted or unsubstituted. The aromatic acids can also be heterocyclic or carbocyclic,monocyclic or polycyclic, substituted or unsubstituted. Suitable substituents are preferably inert to the reaction

conditions in preparing the compounds and include, for example, alkyl, halogen (such as chlorine, bromine, or iodine), alkoxy, alkylthio, alkylamine, nitro, esters, amides, for example. A preferred acyl group is acetyloxy or naphthoyloxy.

The compounds of formula I possess several chiral centers including at carbons 1, 3, 5, 10, 11, 13 and 17. The invention includes racemic compositions and resolved or purified enantiomers. It is preferred that the chirality of the compounds correspond to that possessed by ouabegenin and ouabain. Ouabegenin corresponds to the compound of formula 1 wherein each R group is hydroxy while ouabain corresponds to the compound of formula I wherein R2 is rhamnosyl and R1, R3, R4, R5 and R6 are hydroxy.

Compounds have now been prepared which possess a positive inotropic effect on cardiac muscle cells (i.e., myocytes), as mentioned above. "Positive inotropic effect" means that the contractility of the cells is enhanced in a dose-dependent manner.

A positive inotropic effect-producing amount of the compounds can be administered to a "mammalian host" (e.g., a human) to treat cardiac malfunction (e.g., congestive heart failure, paroxysmal atrial tachycardia, atrial fibrillation and flutter). Administration can be either enteral (i.e., oral) or parenteral (e.g., via intravenous, subcutaneous or intramuscular injection).

In general, the amplitude of contraction (i.e., degree of positive inotropy) can be measured in single, beating myocytes as the amplitude of systolic motion (ASM) using a phase contrast video motion detector system. The same detector system can be used to measure toxicity, which is evidenced as a decrease in ASM, a change in the position of maximal relaxation (MR), and an increase in beating frequency.

In addition to its use in treating cardiac malfunction, a pharmaceutical composition of the compounds can be administered (e.g., enterally or parenterally) to treat patients with serious or life-threatening cardiac glycoside intoxication. Currently, cardiac glycoside intoxication is treated either generally by administering potassium or antiarrhythmic drugs to the patient, or specifically by administering antibody fragments to specific cardiac glycoside preparations. Patients with severe toxicity may be unresponsive to general methods of treatment. In addition, although treatment with antibody fragments does neutralize cardiac glycosides in circulation, the antibodies may not effect cardiac glycosides that are bound to cardiac tissue. Furthermore, because antibodies are proteins, they are administered intravenously and can cause allergic reactions.

In contrast, the described compounds may not only block circulating cardiac glycosides from binding to the Na^+, K^+-ATPase, but also elute or "chase" previously bound cardiac glycoside from Na^+, K^+-ATPase, presumably by competing with or interfering with the cardiac glycoside binding site. "Chase" experiments can be performed using an assay system whereby purified Na^+, K^+-ATPase is reconstituted into liposomes (Anner, B.M. and M. Moosmayer, Biochem. Biophys. Res. Commun., 129:102-108 (1985)).

The detailed protocol for these experiments is set forth in Example IV, and results presented in Table 3 in copending application Serial No. 08/338,264, filed November 10, 1994, the contents of which are incorporated herein by reference in their entirety. In general, liposomes containing functional Na^+, K^+-ATPase molecules were incubated with ^3H-ouabain which permits measurement of specific ouabain binding to its binding site on the Na^+, K^+-ATPase. The liposome-Na^+, K^+-ATPase-ouabain complex was then exposed to varying doses of a compound for 10 minutes at

25°C. The bound ^{3}H-ouabain was eluted from the Na^+, K^+-ATPase by the compound in a dose-dependent manner.

Treatment of cardiac glycoside intoxication with the compound may serve as a highly specific therapy to rapidly reverse the toxic effects on the heart. In addition, as a non-peptide, oral administration of the compounds is possible.

The compounds can also be administered (e.g., enterally or parenterally) to treat blood pressure abnormalities. Studies have shown that excess of endogenous circulating inhibitor of Na^+, K^+-ATPase may be responsible for essential hypertension in some or many patients. (DeWardener, H.E. and G.W. MacGregor, Kidney Int., 18:1-9 (1980)). Presumably, the increased intracellular calcium ion concentration resulting from the binding of an inhibitor to Na^+, K^+-ATPase produces blood vessel constriction and hypertension (Blaustein, M.P., Am. J. Physiol., 232:C165-C173 (1977)).

Experiments can be conducted to determine the vasoconstrictive properties of the compounds. The protocol for these experiments is described in greater detail in Example V of Serial No. 08/338,264. In general, Sprague-Dawley rats can be anesthetized and the abdominal aorta surgically removed. 2 mm vascular rings can be attached to a force transducer and bathed in buffer, and tension adjusted to 1.5 g. Tissue viability can be documented and vasoconstrictive responses calibrated using known vasoconstrictors such as potassium chloride and norepinephrine. Blood vessels thus prepared can then be tested with varying doses of the compound.

The compounds can produce potent, reversible vasoconstriction of the vessels, and these responses can be dose dependent. Vessels remaining viable after exposure to the compound can indicate the absence of toxic effects. Maximum vasoconstrictive responses were similar to those

produced by the known vasoconstrictor substances used as standards.

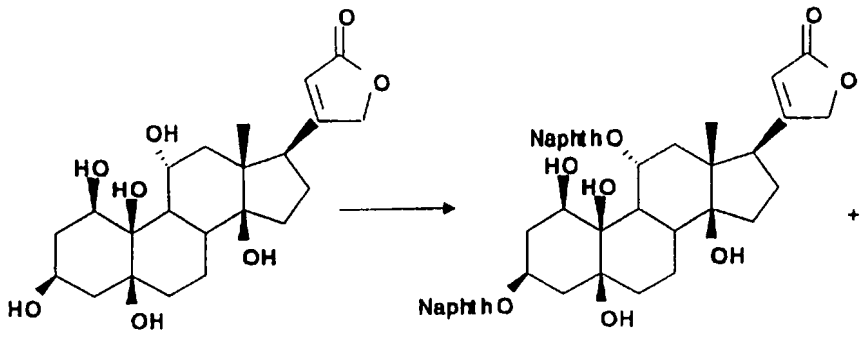
Hypotension, abnormally low blood pressure, can be caused by low cardiac output, inadequate vascular constriction, or both occurring simultaneously. Where the compound has been demonstrated to both increase the strength of cardiac cell contraction and promote blood vessel constriction, its administration in therapeutic amounts would be an effective treatment for hypotension.

Experiments can further be conducted to determine the vasoconstrictive effects of the compound on Sprague-Dawley rat and spontaneously hypertension rat (SHR) pulmonary artery tissue and abdominal aorta tissue. The protocol for these experiments is described in greater detail in Example VI of Serial No. 08/338,264. In general, Sprague-Dawley rats or SHR can be anesthetized and the pulmonary artery (PA) and abdominal aorta (AO) surgically removed. 2-3 mm vascular rings can be cut from these tissues, attached to a force transducer and bathed in buffer. The tension in the transducer can be adjusted to 1.5 g. Tissue viability can be documented and vasoconstrictive responses calibrated using known vasoconstrictors such as potassium chloride and norepinephrine. The response to the compound of blood vessels thus prepared can be compared.

The compounds can also be used to develop specific therapies to prevent excessive vasoconstriction and resulting hypertension. Such therapies would include but not be limited to: (1) Administering antibodies to the compound for passive immunizations; (2) administering immunogenic forms of the compound for active immunity against hypertension; and (3) administering analogues of the compound which could prevent or modulate binding of endogenous Na^+, K^+-ATPase inhibitor, Hypothalamic Inhibitory Factor (HIF) to and action on the vascular or neuronal cell Na^+, K^+-ATPase.

In addition, by potently inhibiting the Na^+, K^+-ATPase activity of renal tubular cells and thereby promoting sodium excretion, a pharmaceutical composition of the compound can be used as a natural diuretic, to promote excretion of excess salt and water by the kidneys in patients suffering from such common clinical conditions as congestive heart failure, cirrhosis of the liver, and nephrotic syndrome. Specific inhibitory effects of the compounds on Na^+, K^+-ATPase support the use of the compound in diuretic therapy without the side effects (e.g., impotence, rashes, blood lipid abnormalities) which commonly occur with existing diuretic drugs.

The compounds can be manufactured, for example, by the processes set forth below:



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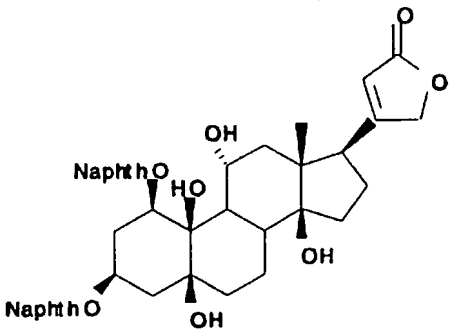
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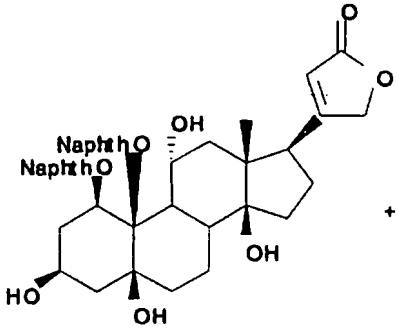
O
OH
NaphthO
HO
OH
NaphthO
OH

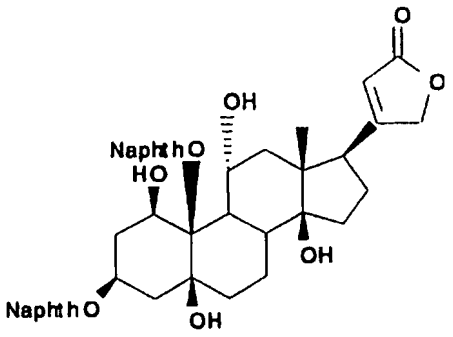
10

+

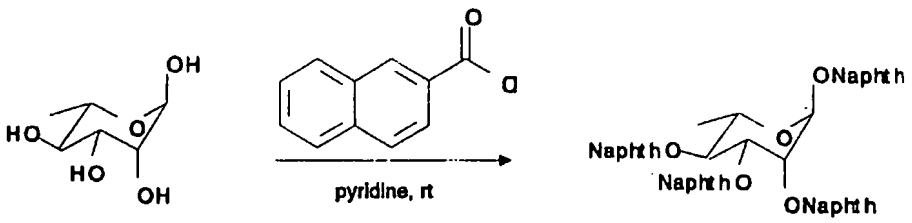

O
O
OH
NaphthO
NaphthO
OH
HO
OH

12

+


O
O
OH
NaphthO
HO
OH
NaphthO
OH

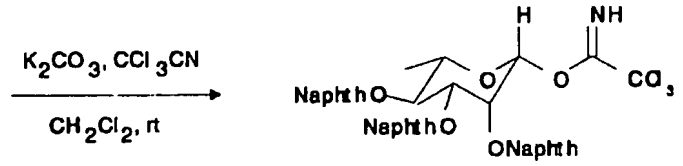
8


OH
HO
O
HO
OH
O
Cl
pyridine, rt
ONaphth
NaphthO
O
NaphthO
ONaphth

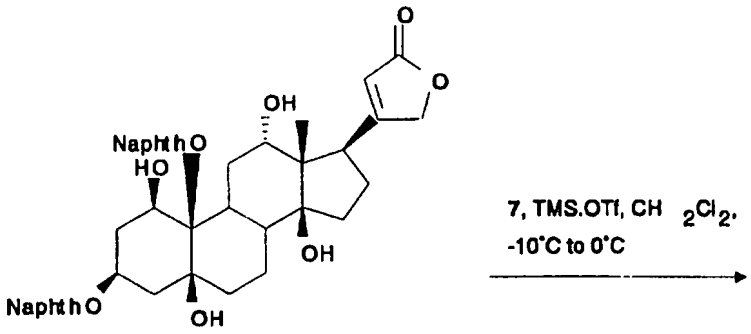
3 5


1. AcBr, MeOH
CH 2Cl2, rt
2. Ag 2CO3,
Wet acetone, rt
ONaphth
NaphthO
O
NaphthO
ONaphth

6


K2CO3, CCl3CN
CH2Cl2, rt
H
NH
O
O
CCl3
NaphthO
NaphthO
ONaphth

7


NaphthO
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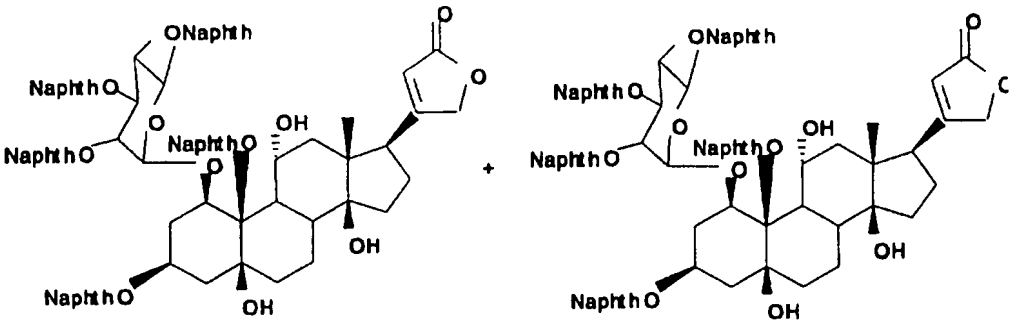
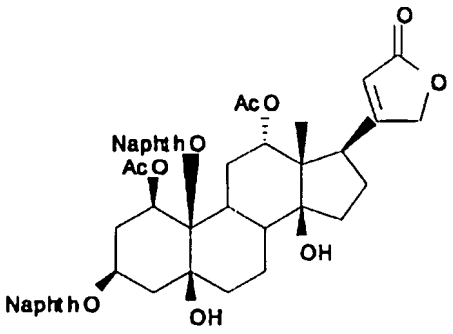
OH
OH
NaphthO
OH
O
O
7, TMS.OTf, CH 2Cl2,
-10°C to 0°C

8

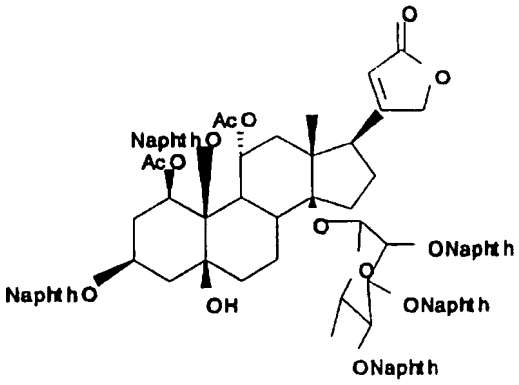

ONaphth
NaphthO
NaphthO
NaphthO
OH
OH
OH
NaphthO
+
ONaphth
NaphthO
NaphthO
NaphthO
OH
OH
OH
NaphthO

15b 22b



9

7, TMS.OTf, CH_2Cl_2,
-10°C to 0°C



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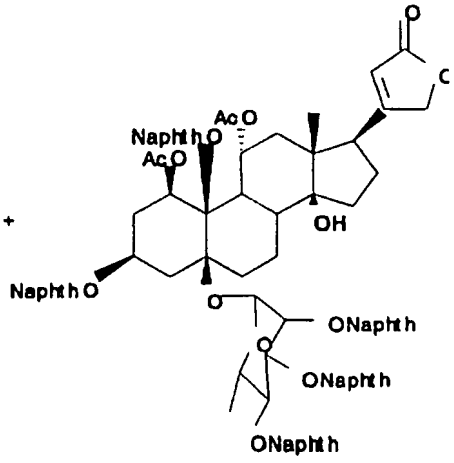

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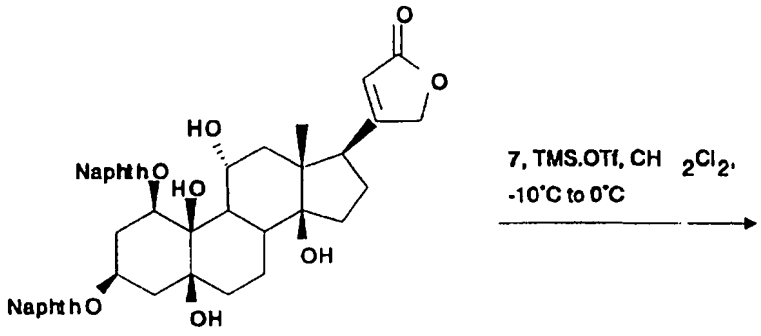
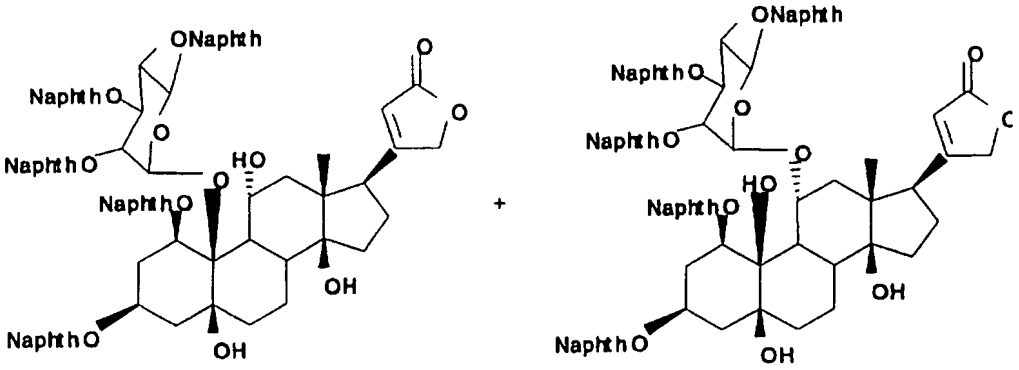

HO
NaphthO
HO
OH
NaphthO
OH
O
O
7, TMS.OTf, CH 2Cl2,
-10°C to 0°C

10


ONaphth
NaphthO
O
NaphthO
HO
O
NaphthO
OH
NaphthO
OH
O
O
+
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NaphthO
O
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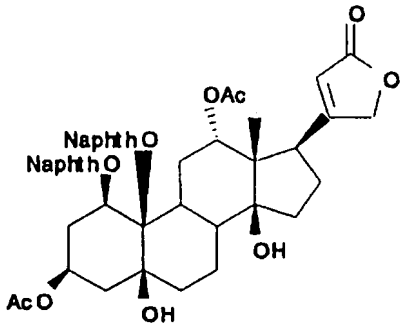
O
HO
NaphthO
OH
NaphthO
OH
O

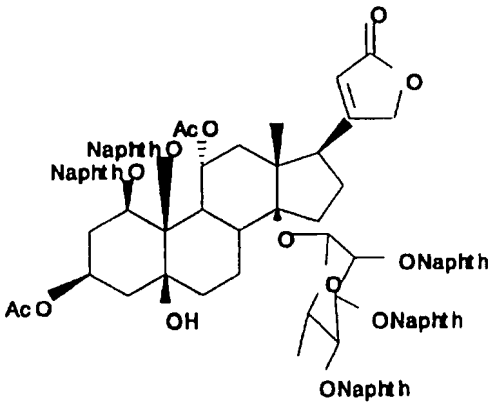
18b

21b



13

7, TMS.OTf, CH_2Cl_2,
-10°C to 0°C



31a

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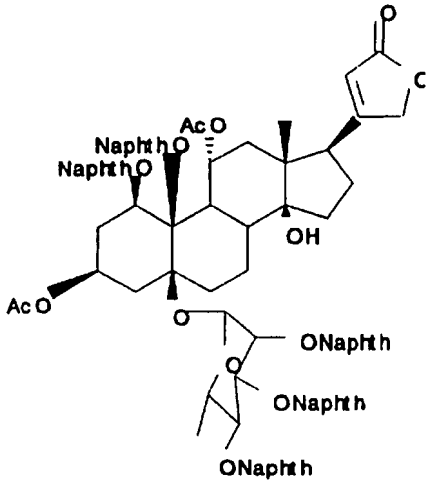

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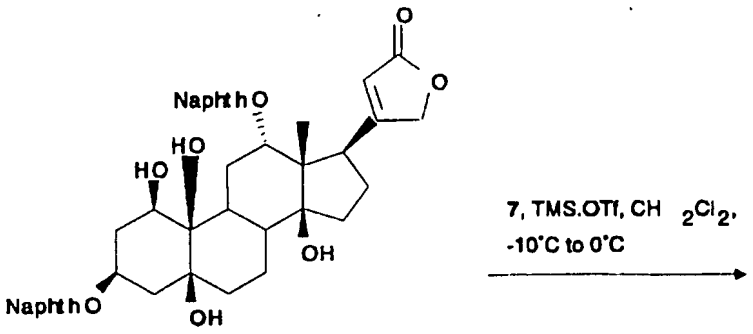

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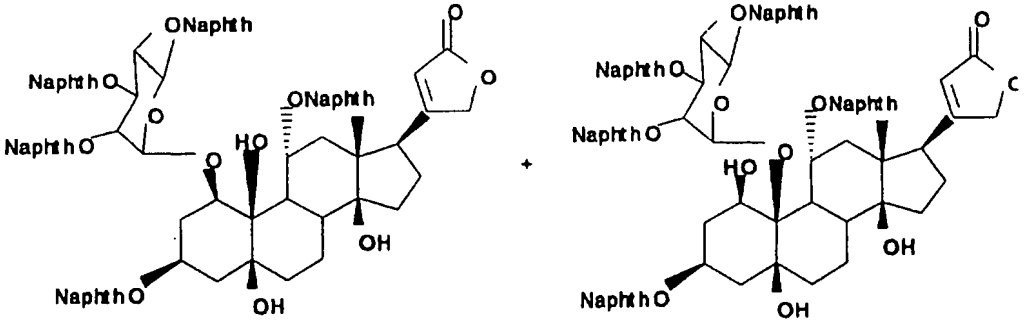


16b 19b

This invention is illustrated further by the following examples, which are not to be construed as limiting in any way.

Experimental Section

All materials were purchased from Aldrich Chemical Company except ouabain and ouabagenin which were purchased from Sigma. Methylene chloride was distilled from calcium hydride under nitrogen. Acetonitrile was Aldrich anhydrous grade. Analytical and preparative TLC was run on precoated silica-gel plates (Analtech, 20 cm x 20 cm, 250 and 500 microns respectively). Analytical and preparative HPLC was performed on Waters HPLC. ^{1}H NMR spectra were recorded on a Bruker 500-MHz spectrometer. UV spectra were taken on a Perkin-Elmer Lambda 6 model. CD analysis was done on a Jasco J-720 spectropolarimeter. All products were further purified by HPLC prior to CD analysis.

Bisnaphthoylation of ouabagenin 2

A mixture of ouabagenin **2** (25 mg, 0.057 mmol), naphthoylimidazole **4** (27 mg, 0.122 mmol) and DBU (35 μL, 0.234 mmol) in 4 mL MeCN was stirred at room temperature for 10 minutes. It was then quenched with water and extracted with CH_2Cl_2. The crude mixture contained four bisnaphthoates 3,19-bis-*O*-naphthoyl-ouabagenin **8**, 1,3-bis-*O*-naphthoyl-ouabagenin **10**, 1,19-bis-*O*-naphthoyl-ouabagenin **12**, and 3,11-bis-*O*-naphthoyl-ouabagenin **14** which were purified by silica gel plate chromatography (39:1 $CHCl_3$/MeOH).

3,19-Bis-*O*-naphthoyl-ouabagenin 8

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.59 (s, 1H), 8.07-8.02 (m, 2H), 7.95-7.83 (m, 6H), 7.62-7.49 (m, 4H), 5.86 (s, 1H, H-22), 5.62 (s, 1H, H-3), 5.50 (d, J = 12.60 Hz, 1H, H-19), 5.48 (s, 1H, H-1), 5.22 (s, 1H), 5.04 (d, J = 12.43 Hz, 1H, H-19), 4.93 (d, J = 16.98 Hz, 1H, H-21), 4.76 (d, J = 18.04 Hz, 1H, H-21), 4.25-4.22 (m, 1H, H-11), 3.64 (bs, 1H), 2.81-2.80 (m, 1H), 2.48-1.14 (m, 16H), 0.96 (s, 3H, H-18).

1,3-Bis-*O*-naphthoyl-ouabagenin 10

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.15 (s, 1H), 7.85 (d, J = 10.18 Hz, 1H), 7.67-7.64 (m, 2H), 7.56 (d, J = 8.20 Hz, 1H), 7.52-7.48 (m, 4H), 7.38-7.31 (m, 2H), 7.09-7.00 (m, 2H), 6.82 (s, 1H, H-1), 5.90 (s, 1H, H-22), 5.60 (s, 1H, H-3), 4.93 (d, J = 18.00 Hz, 1H, H-21), 4.78 (dd, J = 17.98 Hz, J = 1.6 Hz, 1H, H-21), 4.63 (d, J = 11.45 Hz, 1H, H-19), 4.40-4.34 (m, 1H, H-11), 4.28 (s, 1H), 4.22 (d, J = 11.58 Hz, 1H, H-19), 2.87-2.83 (m, 1H), 2.77-2.74 (m, 1H), 2.48-1.24 (m,15H), 0.98 (s, 3H, H-18).

1,19-Bis-*O*-naphthoyl-ouabagenin 12

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.47 (s, 1H), 7.97-7.91 (m, 3H), 7.83-7.72 (m, 5H), 7.56-7.42 (m, 4H), 7.17 (s, 1H, H-1), 5.82 (s, 1H, H-22), 5.25 (d, J = 11.94 Hz, 1H, H-19), 5.14 (d, J = 11.96 Hz, 1H, H-19), 4.94 (s, 1H), 4.86 (dd, J = 17.98 Hz, J = 1.13 Hz, 1H, H-21), 4.71 (dd, J = 17.94 Hz, J = 1.38 Hz, 1H, H-21), 4.46 (s, 1H, H-3), 4.06-4.02 (m, 1H, H-11), 2.76-2.75 (m, 1H), 2.47-1.23 (m, 16H), 0.81 (s, 3H, H-18).

3,11-Bis-*O*-naphthoyl-ouabagenin 14

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.49 (s, 1H), 7.99-7.79 (m, 3H), 7.59-7.48 (m, 5H), 5.88 (s, 1H, H-22), 5.69 (s, 1H, H-3), 5.56 (m, 1H, H-11), 4.91 (s, 1H, H-1), 4.86 (d, J = 17.87 Hz, 1H, H-21), 4.76 (d, J = 18.18 Hz, 1H, H-21), 4.63 (d, J = 11.27 Hz, 1H, H-19), 4.20 (d, J = 11.37 Hz, 1H, H-19), 3.81 (s, 1H), 2.80-1.37 (m, 17H), 1.08 (s, 3H, H-18).

General Acetylation procedure

A mixture of 1,3-bis-*O*-naphthoyl-ouabagenin **10** (3.3 mg, 0.004 mmol), Ac_2O (0.01 mL, 0.13 mmol) and pyridine (0.04 mL, 0.44 mmol) was stirred overnight. It was then quenched with water, extracted with CH_2Cl_2 and the

organic phase was washed three times with saturated aqueous solution of $CuSO_4$. Evaporation of the solvent and purification by silica gel plate chromatography (39:1 $CHCl_3$/MeOH) gave pure 11,19-bis-*O*-acetyl-1,3-bis-*O*-naphthoyl-ouabagenin 11. ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.04 (s, 1H), 7.79 (d, J = 8.59 Hz, 1H), 7.74 (d, J = 8.42 Hz, 1H), 7.69 (d, J = 8.12 Hz, 1H), 7.60 (d, J = 8.57 Hz, 1H), 7.57-7.52 (m, 2H), 7.45-7.42 (m, 2H), 7.31 (t, J = 6.96 Hz, 1H), 7.10 (d, J = 8.72 Hz, 1H), 6.98 (t, J = 7.28 Hz, 1H), 6.85 (d, J = 8.36 Hz, 1H), 6.40 (s, 1H, H-1), 5.91 (s, 1H, H-22), 5.64 (s, 1H, H-3), 5.19 (d, J = 12.18 Hz, 1H, H-19), 5.13-5.08 (m, 1H, H-11), 4.90 (d, J = 18.03 Hz, 1H, H-21), 4.78 (d, J = 18.12 Hz, 1H, H-21), 4.59 (d, J = 12.01 Hz, 1H, H-19), 4.35 (s, 1H), 2.79-2.72 (m, 2H), 2.51-2.44 (m, 2H), 2.27 (s, 3H, CH_3CO), 2.24-1.84 (m, 7H), 1.76 (s, 3H, CH_3CO), 1.74-1.06 (m), 6H, 1.01 (s, 3H, H-18).

1,11-Bis-*O*-acetyl-3,19-bis-*O*-naphthoyl-ouabagenin 9

^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.47 (s, 1H), 8.07-7.82 (m, 8H), 7.61-7.50 (m, 4H), 6.22 (s, 1H, H-1), 5.87 (s, 1H, H-22), 5.67 (s, 1H, H-3), 5.23-5.19 (m, 2H, H-19, H-11), 5.05 (d, J = 12.45 Hz, 1H, H-19), 4.85 (dd, J = 17.98 Hz, J = 1.26 Hz, 1H, H-21), 4.73 (dd, J = 17.94 Hz, J = 1.48 Hz, 1H, H-21), 4.26 (s, 1H), 2.73-2.71 (m, 1H), 2.54-2.39 (m, 3H), 2.21-1.01 (m, 13H), 2.07 (s, 3H, CH_3CO), 1.71 (s, 3H, CH_3CO), 0.94 (s, 3H, H-18).

3,11-Bis-*O*-acetyl-1,19-bis-*O*-naphthoyl-ouabagenin 13

^1H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.35 (s, 1H), 7.95-7.73 (m, 8H), 7.57-7.48 (m, 4H), 6.48 (s, 1H, H-1), 5.86 (s, 1H, H-22), 5.42 (s, 1H, H-3), 5.29-5.14 (m, 3H, H-19, H-19, H-11), 4.85 (dd, J = 17.80 Hz, J = 1.68 Hz, 1H, H-21), 4.73 (dd, J = 17.92 Hz, J = 1.61 Hz, 1H, H-21), 4.37 (s, 1H), 2.73-2.71 (m, 1H), 2.58-2.54 (m, 1H), 2.45-2.35

(m, 2H), 2.13 (s, 3H, CH_3CO), 2.20-1.34 (m, 13H), 1.60 (s, 3H, CH_3CO), 0.94 (s, 3H, H-18).

1,2,3,4-Tetra-*O*-naphthoyl-rhamnopyranose 5

A mixture of rhamnose (400 mg, 2.19 mmol) and naphthoyl chloride (2,600 mg, 13.63 mmol) in anhydrous pyridine (6 mL, 74.18 mmol) was stirred at room temperature overnight. It was then quenched with water and extracted with CH_2Cl_2. The organic layer was washed three times with a saturated aqueous solution of Cu_2SO_4 and dried with Na_2SO_4. Column chromatography of the crude mixture at room temperature the pure product as a white solid (457 mg, 54% yield).

2,3,4-Tri-*O*-naphthoyl-rhamnopyranose 6

A mixture of 5 (457 mg, 0.59 mmol), methyl alcohol (0.19 mL mg, 4.58 mmol) and AcBr (0.4 mL, 5.35 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 1 hour. It was then quenched with water and extracted with Et_2O. The organic layer was dried with Na_2SO_4 and the solvent was evaporated to give the crude bromide which was treated with acetone (4 mL), a drop of water and Ag_2CO_3 (600 mg, 2.18 mmol). Removal of Ag_2CO_3 by gravity filtration and evaporation of the solvent after room temperature almost pure compound **6** as a fluffy white solid (98 mg, 27% yield in two steps).

2,3,4-Tri-*O*-naphthoyl-β-L-rhamnopyranose 1-*O*-trichloro-acetimidate 7

A mixture of 6 (33 mg, 0.05 mmol) and K_2CO_3 (37 mg, 0.27 mmol) in CH_2Cl_2 (1 mL) was stirred at room temperature for 10 minutes at which point CCL_3 CN (0.029 mL, 0.29 mmol) was added and the resulting mixture was stirred for 3 hours. The solvent was then evaporated and the crude

product was directly chromatographed to give pure compound 7 as a fluffy white solid (30 mg, 78% yield).

Glycosylation of 3,19-bis-*O*-naphthoyl-ouabagenin 8

A mixture of 3,19-bis-*O*-naphthoyl-ouabagenin **8** (15 mg, 0.02 mmol) and 4-Å molecular sieves in CH_2Cl_2 (0.8 mL) was stirred for 10 minutes at room temperature and then cooled to -10°C. A solution of 2,3,4-tri-*O*-naphthoyl-β-L-rhamnopyranose 1-*O*-trichloroacetimidate (16 mg, 0.02 mmol) in CH_2Cl_2 (0.2 mL) was added and the mixture was stirred for an additional 10 minutes. TMS.OTf (0.001 μL, 0.006 mmol) diluted in CH_2Cl_2 (11 μL) was then added and the reaction was almost instant, yielding rhamnosides **15b** and **22b**. The mixture was stirred for 15 minutes at -10°C and then was warmed up to 0°C over a 20 minute period. It was then quenched with H_2O, extracted with CH_2Cl_2 and dried over Na_2SO_4. The two regioisomers were separated by plate chromatography (silica gel, 19:1 $CHCl_3$, MeOH).

(1β,3β,5β,11α)-3,19-Bis-*O*-naphthoyl-1-[2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5,11,14-trihydroxy-ouabagenin 15b

^1H NMR (500 MHz,b $CDCl_3$) δ 8.65 (s, 1H), 8.57 (s, 1H), 8.55 (s, 1H), 8.32 (s, 1H), 8.31 (s, 1H), 8.13-7.32 (m, 29H), 7.03 (t, 1H), 5.98 (s, 1H, H-22), 5.80 (s, 1H, H-3), 5.75 (d, J = 15.02 Hz, 1H, H-19), 5.73 (dd, J = 9.66 Hz, J = 3.89 Hz, 1H, H-3'), 5.64 (t, J = 9.8 Hz, 1H, H-4'), 5.40 (s, 1H, H-2'), 5.27 (s, 1H, H-1), 5.12 (d, J = 12.93 Hz, 1H, H-19), 4.97 (d, J = 18.61 Hz, 1H, H-21), 4.83 (d, J = 17.99 Hz, 1H, H-21), 4.61-4.58 (m, 1H, H-11), 4.08-4.02 (m, 1H, H-5'), 2.95-2.93 (m, 1H), 2.69-2.58 (m, 3H), 2.29-1.24 (m, 13H), 1.19 (d, J = 6.13 Hz, 3H, H-6'), 1.09 (s, 3H, H-18). MS (FAB) m/z 1356.

(1β,3β,5β,11α)-3,19-Bis-*O*-naphthoyl-11-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-1,5,14-trihydroxy-ouabagenin 22b

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.54 (s, 1H), 8.34 (s, 1H), 8.32 (s, 1H), 8.12-7.30 (m, 28H), 7.01-6.83 (m, 3H), 5.94 (s, 1H, H-3), 5.80-5.75 (m, 3H, H-22, H-2', H-1), 5.54-5.48 (m, 2H, H-4', H-19), 5.38-5.28 (m, 3H, H-3', H-19, H-1'), 4.84 (d, J = 18.28 Hz, 1H, H-21), 4.467 (dd, J = 18.75 Hz, J = 1.43 Hz, 1H, H-21), 4.33-4.27 (m, 2H, H-11, H-5'), 2.90-2.87 (m, 1H), 2.72-2.54 (m, 3H), 2.18-1.42 (m, 13H), 0.99 (d, J = 6.15 Hz, 3H, H-6'), 0.67 (s, 3H, H-18). MS (FAB) m/z 1356.

Glycosylation of 1,11-bis-*O*-acetyl-3,19-bis-*O*-naphthoyl-ouabagenin 9

A mixture of 1,11-bis-*O*-acetyl-3,19-bis-*O*-naphthoyl-ouabagenin **9** (5 mg, 0.006 mmol) and 4-Å molecular sieves in CH_2Cl_2 (0.2 mL) was stirred for 10 minutes at room temperature and then cooled to -10°C. A solution of 2,3,4-tri-*O*-naphthoyl-β-L-rhamnopyranose 1-*O*-trichloroacetimidate (5 mg, 0.006 mmol) in CH_2Cl_2 (0.4 mL) was added and the mixture was stirred for an additional 10 minutes. TMS.OTf (0.002 μL, 3.5 x 10^{-4} mmol) diluted in CH_2Cl_2 (14 μL) was then added and the reaction was almost instant, yielding rhamnosides **30a** and **25a**. The mixture was stirred for 15 minutes at -10°C and then was warmed up to 0°C over a 20 minute period. It was then quenched with H_2O, extracted with CH_2Cl_2 and dried over Na_2SO_4. The two regioisomers were separated by plate chromatography (silica gel, 19:1 $CHCl_3$, MeOH).

(1β,3β,5β,11α)-1,11-Bis-*O*-acetyl-3,19-bis-*O*-naphthoyl-5-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-14-hydroxy-ouabagenin 30a

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.66 (s, 1H), 8.62 (s, 1H), 8.52 (s, 1H), 8.40 (s, 1H), 8.14-7.35 (m, 30H), 6.00 (s, 1H, H-22), 5.96 (t, J = 9.84 Hz, 1H, H-4'), 5.92 (bs, 1H, H-11), 5.84 (dd, J = 10.18 Hz, J = 3.36 Hz, 1H, H-3'), 5.80 (s, 1H, H-1), 5.68 (s, 1H, H-3), 5.59 (s, 1H, H-2'), 5.46 (s, 1H, H-1'), 5.41 (d, J = 12.27 Hz, 1H, H-19), 4.98 (d, J = 12.42 Hz, 1H, H-19), 4.87 (d, J = 17.5 Hz, 1H, H-21), 4.80 (d, J = 17.58 Hz, 1H, H-21), 4.45-4.42 (m, 1H, H-5'), 3.06 (bs, 1H), 2.59-1.52 (m, 16H), 2.18 (s, 1H, CH_3CO), 1.64 (s, 1H, CH_3CO), 1.47 (d, J = 6.14 Hz, 3H, H-6'), 1.13 (s, 3H, H-18). MS (FAB) m/z 1461.

(1β,3β,5β,11α)-1,11-Bis-*O*-acetyl-3,19-bis-*O*-naphthoyl-14-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5-trihydroxy-ouabagenin 25a

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.65 (s, 1H), 8.54 (s, 1H), 8.52 (s, 1H), 8.42 (s, 1H), 8.10-7.33 (m, 30H), 6.35 (s, 1H, H-1), 5.98 (t, J = 10.00 Hz, 1H, H-4'), 5.94 (s, 1H, H-22), 5.89 (dd, J = 10.30 Hz, J = 3.10 Hz, 1H, H-3'), 5.54 (s, 1H, H-3), 5.40 (s, 1H, H-2'), 5.32 (s, 1H, H-1'), 5.30-5.27 (m, 2H, H-19, H-11), 5.17 (d, J = 10.09 Hz, 1H, H-19), 4.90 (s, 2H, H-21), 4.46-4.36 (m, 1H, H-5'), 4.28 (s, 1H), 3.47-3.45 (bs, 1H), 3.36-3.32 (app t, 1H), 2.61-1.48 (m, 15H), 2.12 (s, 1H, CH_3CO), 1.73 (s, 1H, CH_3CO), 1.44 (d, J = 6.24 Hz, 3H, H-6'), 1.33 (s, 3H, H-18). MS (FAB) m/z 1461.

Glycosylation of 1,3-bis-*O*-naphthoyl-ouabagenin 10

A mixture of 1,3-bis-*O*-naphthoyl-ouabagenin 10 (8.7 mg, 0.012 mmol) and 4-Å molecular sieves in CH_2Cl_2 (0.4 ml) was stirred for 10 minutes at room temperature and then cooled to -10°C. A solution of 2,3,4-tri-*O*-naphthoyl-

β-L-rhamnopyranose 1-*O*-trichloroacetimidate (9 mg, 0.012 mmol) in CH_2Cl_2 (0.2 mL) was added and the mixture was stirred for an additional 10 minutes. TMS.OTf (0.003 μL, 6.7 x 10^{-4} mmol) diluted in CH_2Cl_2 (13 μL) was then added and the reaction was almost instant, yielding rhamnosides **18b** and **21b**. The mixture was stirred for 15 minutes at -10°C and then was warmed up to 0°C over a 20 minute period. It was then quenched with H_2O, extracted with CH_2Cl_2 and dried over Na_2SO_4. The two regioisomers were separated by plate chromatography (silica gel, 19:1 $CHCl_3$, MeOH).

(1β,3β,5β,11α)-1,3-Bis-*O*-naphthoyl-19-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5,11,14-trihydroxy-ouabagenin 18b

^1H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.65 (s, 1H), 8.58 (s, 1H), 8.44 (s, 1H), 8.31-7.27 (m, 29H), 7.01-6.90 (m, 2H), 6.71 (s, 1H, H-1'), 6.33 (dd, J = 10.13 Hz, J = 3.40 Hz, 1H, H-3'), 5.98 (t, J = 9.92 Hz, 1H, H-4'), 5.94 (s, 1H, H-22), 5.91 (s, 1H, H-2'), 5.84-5.80 (bs, 1H, H-3), 5.39 (s, 1H, H-1'), 4.97-4.89 (m, 2H, H-11, H-21), 4.82 (d, J = 18.11 Hz, 1H, H-21), 4.76 (d, J = 11.06 Hz, 1H, H-19), 4.64-4.61 (m, 1H, H-5'), 4.37 (d, J = 9.54 Hz, 1H, H-19), 3.24-3.21 (m, 1H), 2.97-2.94 (m, 1H), 2.84-2.80 (m, 1H), 2.66-2.61 (m, 1H), 2.30-1.53 (m, 13H), 1.50 (d, J = 6.12 Hz, 3H, H-6'), 0.98 (s, 3H, H-18). MS (FAB) m/z.

(1β,3β,5β,11α)-1,3-Bis-*O*-naphthoyl-11-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5,14,19-trihydroxy-ouabagenin 21b

^1H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.65 (s, 1H), 8.52 (s, 1H), 8.37 (s, 1H), 8.26 (s, 1H), 8.21-7.27 (m, 27H), 7.07-7.02 (m, 3H), 6.98 (s, 1H, H-1), 6.31 (dd, J = 10.16 Hz, J = 3.47 Hz, 1H, H-3'), 5.95-5.90 (m, 2H, H-4', H-22), 5.89 (dd, J = 3.30 Hz, J = 1.24 Hz, 1H, H-2'),

5.83 (s, 1H, H-3), 5.41 (s, 1H, H-1'), 5.02-4.98 (m, 1H, H-11), 4.94 (d, J = 18.43 Hz, 1H, H-21), 4.81 (dd, J = 19.4 Hz, J = 1.50 Hz, 1H, H-21), 4.83-4.79 (m, 2H, H-19, H-5'), 4.45 (dd, J = 13.84 Hz, J = 9.65 Hz, 1H, H-19), 4.36 (s, 1H), 3.20-3.17 (m, 1H), 2.91-2.81 (m, 2H), 2.70-2.64 (m, 1H), 2.45-1.47 (m, 13H), 1.44 (d, J = 6.17 Hz, 3H, H-6'), 1.01 (s, 3H, H-18). MS (FAB) m/z 1377.

Glycosylation of 3,11-bis-*O*-acetyl-1,19-bis-*O*-naphthoyl-ouabagenin 13

A mixture of 3,11-bis-*O*-acetyl-1,19-bis-*O*-naphthoyl-ouabagenin **13** (8 mg, 0.0096 mmol) and 4-Å molecular sieves in CH_2Cl_2 (0.2 mL) was stirred for 10 minutes at room temperature and then cooled to -10°C. A solution of 2,3,4-tri-*O*-naphthoyl-β-L-rhamnopyranose 1-*O*-trichloroacetimidate (8 mg, 0.0096 mmol) in CH_2Cl_2 (0.2 mL) was added and the mixture was stirred for an additional 10 minutes. TMS.OTf (0.003 μL, 5.6 x 10^{-4} mmol) diluted in CH_2Cl_2 (22 μL) was then added and the reaction was almost instant, yielding rhamnosides **31a** and **27a**. The mixture was stirred for 15 minutes at -10°C and then was warmed up to 0°C over a 20 minutes period. It was then quenched with H_2O, extracted with CH_2Cl_2 and dried over Na_2SO_4. The two regioisomers were separated by plate chromatography (silica gel, 19:1 $CHCl_3$, MeOH).

(1β,3β,5β,11α)-3,11-Bis-*O*-acetyl-1,19-bis-*O*-naphthoyl-5-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-14-hydroxy-ouabagenin 31a

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.63 (s, 1H), 8.54 (s, 1H), 8.41 (s, 1H), 8.36 (s, 1H), 8.30-7.31 (m, 30H), 6.02 (s, 1H, H-1), 6.00 (s, 1H, H-22), 5.96 (t, J = 9.99 Hz, 1H, H-4'), 5.90 (bs, 1H, H-11), 5.85 (dd, J = 10.16 Hz, J = 2.99 Hz, 1H, H-3'), 5.59 (s, 1H, H-2'), 5.49 (d, J = 12.40 Hz, 1H, H-19), 5.46 (s, 1H, H-1'), 5.43

(s, 1H, H-3), 4.97 (d, J = 12.11 Hz, 1H, H-19), 4.87 (d, J = 17.16 Hz, 1H, H-21), 4.80 (d, J = 17.41 Hz, 1H, H-21), 4.47-4.42 (m, 1H, H-5'), 4.22 (s, 1H), 3.05-3.00 (m, 1H) 2.60-1.65 (m, 16H), 2.25 (s, 1H, CH_3CO), 1.60 (s, 1H, CH_3CO), 1.48 (d, J = 6.13 Hz, 3H, H-6'), 1.13 (s, 3H, H-18). MS (FAB) m/z 1462.

(1β,3β,5β,11α)-3,11-Bis-*O*-acetyl-1,19-bis-*O*-naphthoyl-14-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5-trihydroxy-ouabagenin 27a

^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.66 (s, 1H), 8.46 (s, 1H), 8.42 (s, 1H), 8.41 (s,1H), 8.11-7.38 (m, 30H), 6.55 (s, 1H, H-1), 5.99 (t, J = 10.00 Hz, 1H, H-4'), 5.91 (s, 1H, H-22), 5.89 (dd, J = 10.36 Hz, J = 3.12 Hz, 1H, H-3'), 5.55 (s, 1H, H-2'), 5.45 (s, 1H, H-3), 5.34 (s, 1H, H-1'), 5.31 (s, 2H, H-19), 5.28-5.23 (m, 1H, H-11), 4.92 (s, 2H, H-21), 4.48-4.42 (m, 1H, H-5'), 4.40 (s, 1H), 3.37-3.33 (app t, 1H), 2.61-1.52 (m, 16H), 2.19 (s, 1H, CH_3CO), 1.61 (s, 1H, CH_3CO), 1.46 (d, J = 6.21 Hz, 3H, H-6'), 1.39 (s, 3H, H-18). MS (FAB) m/z 1462.

Glycosylation of 3,11-bis-*O*-naphthoyl-ouabageinin 14

A mixture of 3,11-bis-*O*-naphthoyl-ouabagenin **14** (21 mg, 0.03 mmol) and 4-Å molecular sieves in CH_2Cl_2 (1.2 mL) was stirred for 10 minutes at room temperature and then cooled to -10°C. A solution of 2,3,4-tri-*O*-naphthoyl-β-L-rhamnopyranose 1-*O*-trichloroacetimidate (22 mg, 0.03 mmol) in CH_2Cl_2 (0.4 mL) was added and the mixture was stirred for an additional 10 minutes. TMS.OTf (0.002 μL, 0.008 mmol) diluted in CH_2Cl_2 (16 μL) was then added and the reaction was almost instant, yielding rhamnosides **16b** and **19b**. The mixture was stirred for 15 minutes at -10°C and then was warmed up to 0°C over a 20 minute period. It was then quenched with H_2O, extracted with CH_2Cl_2 and dried

over Na_2SO_4. The two regioisomers were separated by plate chromatography (silica gel, 19:1 $CHCl_3$, MeOH).

(1β,3β,5β,11α)-3,11-Bis-O-naphthoyl-1-[(2,3,4-tri-O-naphthoyl-α-L-rhamnopyranosyl)oxy]-5,14,19-trihydroxy-ouabagenin 16b

^1H NMR (500 MHz, $CDCl_3$ δ 8.52 (s, 1H), 8.48 (s, 1H), 8.42 (s, 1H), 8.19 (s, 1H), 7.92-6.86 (m, 31H), 5.90 (bs, 2H, H-11, H-22), 5.80 (bs, 1H, H-3), 5.61 (dd, J = 10.07 Hz, J = 3.31 Hz, 1H, H-3'), 5.32 (t, J = 10.05 Hz, 1H, H-4'), 5.20 (s, 1H, H-1), 5.13 (d, J = 2.03 Hz, 1H, H-2'), 4.89 (d, J = 18.13 Hz, 1H, H-21), 4.79 (d, J = 17.84 Hz, 1H, H-21), 4.73 (d, J = 11.40 Hz, 1H, H-19), 4.66 (s, 1H, H-1'), 4.52 (s, 1H), 4.37 (d, J = 11.85 Hz, 1H, H-19), 4.29-4.23 (m, 1H, H-5'), 2.92-1.19 (m, 17H), 1.60 (s, 3H, H-18), 0.96 (d, J = 6.20 Hz, 3H, H-6'). MS (FAB) m/z 1355.

(1β,3β,5β,11α)-3,11-Bis-O-naphthoyl-19-[(2,3,4-tri-O-naphthoyl-α-L-rhamnopyranosyl)oxy]-1,5,14-trihydroxy-ouabagenin 19b

^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.58 (s, 1H), 8.53 (s, 1H), 8.49 (s, 1H), 8.33 (s, 1H), 8.16-7.18 (m, 30H), 6.07 (dd, J = 10.20 Hz, J = 3.27 Hz, 1H, H-3'), 5.98-5.93 (m, 1H, H-11), 5.91 (s, 1H, H-22), 5.87-5.85 (m, 2H, H-2', H-4'), 5.74 (s, 1H, H-3), 5.26 (d, J = 1.36 Hz, 1H, H-1'), 4.93 (d, J = 18.60 Hz, 1H, H-21), 4.86-4.83 (m, 2H, H-1, H-21), 4.54 (s, 2H, H-19), 4.46-4.41 (m, 1H, H-5'), 2.91-2.90 (m, 1H), 2.64-1.49 (m, 16H), 1.45 (d, J = 6.19 Hz, 3H, H-6'), 1.32 (s, 3H, H-18). MS (FAB) m/z 1355.

HIF (Hypothalamic Inhibitory Factor) is an endogenous cardiotonic factor that has been isolated from bovine hypothalamus. Its structure is believed to carry a close resemblance to that of ouabain **1**, a cardiotonic glycoside of plant origin. These studies of the pentanaphthoyl

derivatives of HIF and Ouabain showed that these compounds have different HPLC retention times and CD spectra, and additionally indicate that these compounds have different structures. While ouabain pentanaphthoate shows a strong positive exciton couplet CD (245 nm ($\Delta\epsilon$ + 209), 229 nm ($\Delta\epsilon$ -170)), HIF pentanaphthoate has no distinct CD Cotton effects. The theoretical CD spectra of all fifteen possible ouabain pentanaphthoate analogs varying the glycosidic linkage in positions 1, 19, 11 and 5 and keeping the genin part intact was calculated. The CD calculations were performed using a combination of molecular modeling and the π-electron SCF-CI-DV MO method. Eight compounds were also synthesized in order to prove the validity of the calculations. In almost all the cases there was a good agreement of theoretical and experimental results.

The following Table summarizes the calculated and observed CD spectra for the each identified compound.

		calcd (π-SCF-CI-DV MO)				obsd (MeCN)			
Entry	Rhamnoside	Compd[a]	UV λ_{max},	CD, λ_{ext}, nm ($\Delta\epsilon$)	A	Compd	UV λ_{max},	CD, λ_{ext}, nm ($\Delta\epsilon$)	A
1	3-R/1,19-N	**1a**	239	251 (243)/233 (-232)	+475	**1b**	233	245 (+209)/229 (-170)	+379
2	1-R/3,19-N	**15a**	235	248 (202)/230 (-75)	+277	**15b**	234	245 (+202)/232 (-78)	+280
3	1-R/3,11-N	**16a**	238	245 (235)/226 (-117)	+352	**16b**	234	245 (+217)/223 (-88)	+305
4	1-R/19,11-N	**17a**	236	253 (95)/235 (-68)	+163	**17b**	--	--	--
5	19-R/3,1-N	**18a**	236	243 (197)/224 (-152)	+349	**18b**	232	244 (+209)/229 (-141)	+350
6	19-R/3,11-N	**19a**	238	248 (-156)/227 (160)	-316	**19b**	235	244 (+148)/228 (-59)	+207
7	19-R/1,11-N	**20a**	240	245 (154)/227 (-93)	+247	**20b**	--	--	--
8	11-R/3,1-N	**21a**	235	245 (149)/228 (-170)	+319	**21b**	231	244 (+209)/229 (-156)	+365
9	11-R/3,19-N	**22a**	238	245 (239)/225 (-116)	+355	**22b**	234	236 (+159)/220 (-56)	+215
10	11-R/1,19-N	**23a**	233	242 (904)/220 (-739)	+1642	**23b**	--	--	--
11	5-R/3,1-N	**24a**	236	250 (180)/232 (-179)	+359	**24a**	--	--	--
12	5-R/3,19-N	**25a**	238	248 (482)/227 (-478)	+960	**25a**	237	244 (+423)/228 (-305)	+728
13	5-R/3,11-N	**26a**	238	248 (179)/228 (-132)	+311	**26a**	--	--	--
14	5-R/1,19-N	**27a**	237	249 (326)/228 (-448)	+773	**27a**	235	243 (+270)/227 (-188)	+458
15	5-R/1,11-N	**28a**	238	242 (107)/216 (-83)	+190	**28a**	--	--	--
16	5-R/11,19-N	**29a**	237	251 (113)/233 (-43)	+156	**29a**	--	--	--
17		**HIF**					233	~0	

[a] Compounds **a** have acetyl groups on all other free hydroxy groups except 14-OH.
Compounds **b** have all other hydroxy groups free

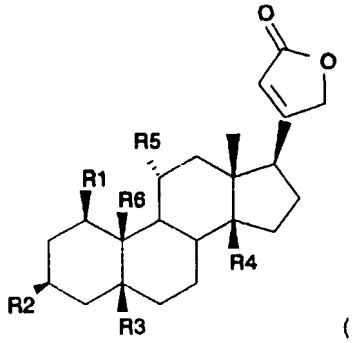
EQUIVALENTS

Those skilled in the art will know, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. These and all other equivalents are intended to be encompassed by the following claims.

CLAIMS

What is claimed is:

1. A compound of the formula:



(I)

wherein each R1, R3, R4, R5 and R6 is independently selected from the group consisting of OH, acyloxy and/or rhamnosyl, at least one of which is rhamnosyl, and R2 is OH or acyloxy.

2. A compound selected from the group consisting of:

(1β,3β,5β,11α)-1,11-Bis-*O*-acetyl-3,19-bis-*O*-naphthoyl-5-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-14-hydroxy-ouabagenin;

(1β,3β,5β,11α)-3,19-Bis-*O*-naphthoyl-11-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-1,5,14-trihydroxy-ouabagenin;

(1β,3β,5β,11α)-3,19-Bis-*O*-naphthoyl-1-[2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5,11,14-trihydroxy-ouabagenin;

(1β,3β,5β,11α)-1,3-Bis-*O*-naphthoyl-19-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5,11,14-trihydroxy-ouabagenin;

(1β,3β,5β,11α)-1,11-Bis-*O*-acetyl-3,19-bis-*O*-naphthoyl-14-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5-trihydroxy-ouabagenin;

(1β,3β,5β,11α)-1,3-Bis-*O*-naphthoyl-11-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5,14,19-trihydroxy-ouabagenin;

(1β,3β,5β,11α)-3,11-Bis-*O*-acetyl-1,19-bis-*O*-naphthoyl-5-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-14-hydroxy-ouabagenin;

(1β,3β,5β,11α)-3,11-Bis-*O*-acetyl-1,19-bis-*O*-naphthoyl-14-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5-trihydroxy-ouabagenin;

(1β,3β,5β,11α)-3,11-Bis-*O*-naphthoyl-1-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-5,14,19-trihydroxy-ouabagenin; and

(1β,3β,5β,11α)-3,11-Bis-*O*-naphthoyl-19-[(2,3,4-tri-*O*-naphthoyl-α-L-rhamnopyranosyl)oxy]-1,5,14-trihydroxy-ouabagenin.

3. A pharmaceutical composition useful for treating mammals with cardiovascular disorders comprising an effective amount of the compound of Claim 1 and a therapeutically acceptable carrier.

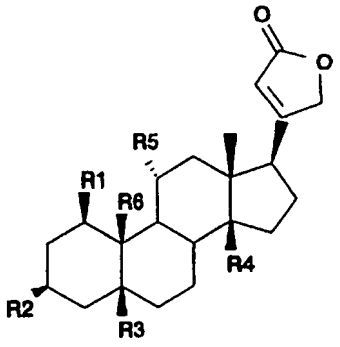
4. A method for altering the activity of Na^+, K^+-ATPase in a mammalian host by administering to the host an effective amount of the compound of Claim 1.

5. A method for producing a positive inotropic effect in a mammalian host by administering to the host a positive inotropic effect-producing amount of the compound of Claim 1.

6. A method of Claim 5 in which the cardiac malfunction is congestive heart failure, paroxysmal atrial tachycardia or atrial fibrillation.

7. A method of treating a mammal with hypotension comprising administering to the mammal an effective amount of the compound of Claim 1.

8. An oaubain derivative or stereoisomer of the formula:



(I)

wherein each R1-R6 is independently selected from the group consisting of OH, acyloxy and/or rhamnosyl, at least one of which is rhamnosyl and stereoisomers thereof.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/US 97/14264

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07J19/00 A61K31/585

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. TEMPLETON ET AL: "Pregnane and 21-Norpregnane Derivatives of Ouabain that Bind to the Digitalis Receptor" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY.CHIMICA THERAPEUTICA., vol. 29, no. 10, 1994, PARIS FR, pages 799-804, XP002047421	8
Y	see page 803; example 1C; table III	1-7
X	L. BROWN ET AL: "Comparison of the Inotropic Potencies of Some Synthetic and Naturally Occurring Cardiac Glycosides Using Isolated Left Atrium of Guinea Pig" ARZNEIMITTEL FORSCHUNG DRUG RESEARCH., vol. 33(I), no. 6, 1983, AULENDORF DE, pages 814-817, XP002047422	8
Y	see page 815; examples 16,17; table 1	1-7

-/--

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 1997	06.01.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Watchorn, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internr al Application No
PCT/US 97/14264

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 124, no. 9, 26 February 1996 Columbus, Ohio, US; abstract no. 117733, KHUSHBAKTOVA Z A ET AL: "Synthesis and biological activity of new strophanthidin derivatives" page 1310; column 2; XP002047425 see abstract & KHIM.-FARM. ZH., vol. 29, no. 8, 1995, pages 22-26, ---	1-8
Y	TAWFIK H ET AL: "Comparative studies of some semisynthetic k-strophanthins with natural cardiac glycosides" BIOCHEMICAL PHARMACOLOGY, vol. 34, no. 14, 1985, pages 2541-2547, XP002047423 see the whole document ---	1-8
Y	MIRSALIKHOVA N M ET AL: "Some features of the inhibition of sodium-potassium ion ATPase in heart muscle by cardiotonic glycosides" NIH PUBL. (NIH-80-2017, ENERGY TRANSP. PROTEIN SYNTH. HORM. CONTROL HEART METAB.,), 1980, pages 269-275, XP002047424 see the whole document -----	1-8

INTERNATIONAL SEARCH REPORT

Ir national application No.
PCT/US 97/ 14264

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 4-7
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.